Title: Prevalence of cardiovascular-related comorbidity in ankylosing spondylitis, psoriatic arthritis and psoriasis in primary care: a matched retrospective cohort study

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Title Prevalence of cardiovascular-related comorbidity in ankylosing spondylitis, psoriatic arthritis and psoriasis in primary care: a matched retrospective cohort study

Abstract

Objective: To compare the prevalence of cardiovascular (CVD)-related comorbidities in patients with ankylosing spondylitis (AS), psoriatic arthritis (PsA) or psoriasis (Ps) in UK primary care against matched cohorts.

Methods: Matched retrospective cohort study using a primary care consultation database. Three cohorts were constructed using all patients with a Read code diagnosis of AS, PsA or Ps between 1999-2009, each cohort was then compared in a 1:4 ratio to a matched cohort. The prevalence of CVD-related comorbidities (hypertension, ischaemic heart disease, hyperlipidaemia and diabetes mellitus) were identified by the first consultation of a comorbid Read code, in those with an inflammatory condition of interest. The prevalence of CVD-related comorbidities was compared between each inflammatory cohort and their matched cohort using Fisher's exact test.

Results: 94 AS, 106 PsA & 290 Ps patients were identified. Compared with matched cohorts, the most prevalent CVD-related comorbidity in patients with AS was hypertension (35 (37.2%) vs. 96 matched (25.5%), p = 0.03), this was also the case for PsA (41 (38.7%) vs. 114 matched (26.9%), p = 0.02). No differences were seen in the prevalence of other CVD-related comorbidities in those with AS, PsA or Ps compared to their matched cohorts.

Conclusion: Our findings provide UK comparisons of CVD-related comorbidities in patients with AS, PsA and Ps alone; specifically demonstrating increased prevalence of hypertension in AS and PsA cohorts compared to their matched cohorts. This further supports the argument for more evidence in the need for screening and intervention around CVD comorbidities in inflammatory conditions.

Keywords:

ankylosing spondylitis; cardiovascular disease; psoriasis; psoriatic arthritis; primary care

Background

The relationship between inflammatory conditions and subsequent development of cardiovascular disease (CVD) has become increasingly established, reflecting the negative effect of systemic inflammation on the vascular system [1]. However, the evidence around this and subsequent impact on clinical guidelines varies between inflammatory conditions. It is well established that patients with rheumatoid arthritis (RA) have an excess risk of CVD morbidity and mortality [2], and this is reflected in UK clinical guidelines advocating annual screening for CVD risk factors in patients with RA to mitigate this excess risk [3, 4]. In contrast, though patients with ankylosing spondylitis (AS) and psoriatic arthritis (PsA) are also believed to be at an increased risk of CVD [5-7], results have shown a mixed profile. To date, most studies have been conducted in secondary care and are therefore more likely to reflect patients with more severe disease and who may be more likely to develop CVD. A lack of primary care research around the risk of AS and PsA populations developing CVD-related comorbidities makes management difficult for general practitioners (GP).

In previous AS research, a Swedish registry cohort found significantly greater standardized morbidity-rate ratios (SMR) for ischaemic heart disease (IHD), hypertension and diabetes mellitus [8]. In a longitudinal primary care population from Wales, AS patients had similar rates of myocardial infarction (MI) and stroke as matched-controls, but hypertension was more prevalent [9]. A Dutch study found an increased prevalence of hypertension in patients with AS compared to the general population [6] and though a second Dutch study found female patients with AS to be at greater risk of developing myocardial infarction, male AS patients were not [10].

Regarding the relationship between PsA and CVD, a 2013 systematic review by Jamnitski et al, found four studies, all reporting an increase in the respective CVD morbidity examined (including IHD, congestive heart failure as well as cerebrovascular and peripheral vascular disease). However, these studies included a diverse range of study designs, including both primary and secondary care populations, and patients with both psoriasis and psoriatic arthritis

[11]. Most recently, a large study from UK primary care found that major adverse cardiovascular events (MACE) were more common in PsA patients not prescribed a disease modifying anti-rheumatic drug (DMARD), but not in those using DMARDS, compared to controls [12].
Our understanding of the prevalence of different CVD-related comorbidities in AS and PsA remains unclear, as does the extent to which psoriasis plays a role in CVD comorbidity experienced by PsA patients' [13]. Therefore, the aim of this study was to compare the prevalence of CVD-related comorbidity in patients with AS, PsA and Ps to matched cohorts free of inflammatory disease in UK primary care. We thus hypothesised that the prevalence of CVD-related comorbidities would be greater in patients with AS, PsA and Ps compared to matched populations.

Methods

Study design & population

We conducted a matched retrospective cohort study using the Consultations in Primary Care Archive (CiPCA), a database that contains all recorded consultation data from a subset of general practices in North Staffordshire, UK [14]. CiPCA is a high-quality primary care database giving results comparable to other UK national databases [14] and has been used to research inflammatory conditions previously [15]. This dataset, which was granted ethical approval by the North Staffordshire Research Ethics Committee, is updated regularly and practices are required to maintain a high standard of consultation recording quality [16]. This ensures that the validity of coding conducted by GPs is at an appropriate level for use within research.
Three cohorts were constructed using all patients aged ≥18 years with a diagnosis of AS, PsA or Ps between 1999 and 2009. Each diagnosis was identified using Read codes, this is the coding system used within primary care and applied by the GP to provide a standard classification of clinical information relating to morbidity and drug therapies (specific codes available on request). Ps patients who also had a PsA Read code were categorised within the PsA cohort.
Each disease cohort was matched exactly by year of birth, gender, general practice and the year

of consultation for the inflammatory condition to a control group in a 1:4 ratio respectively. Control population was randomly selected from the matched individual pool. The outcome of interest was a consultation with a diagnostic Read code for hypertension, IHD (including myocardial infarction and angina), hyperlipidaemia or diabetes mellitus (DM) in the ten-year study period, irrespective of date of inflammatory condition diagnosis. If multiple consultations were made for the sample CVD Read code then the earliest recorded code was used. The choice of CVD-related comorbidities was based on those routinely identified and managed in primary care.

Statistical Analyses

Key characteristics of each of the three cohorts and their matched controls were reported. These included factors upon which the cohorts were matched; age (mean and Standard Deviation (SD), determined from year of birth) and gender. Prevalence of CVD-related comorbidities within each cohort were compared to their matched cohort using Fisher's exact test, with significance regarded as a p-value of <0.05 (two-tailed). All statistical analysis was performed in STATA version 13.

Results

94 AS, 106 PsA & 290 Ps patients were identified and successfully matched to their respective cohort (**Table 1**). We found a significantly higher prevalence of hypertension in both AS and PsA cohorts compared with controls, but not for IHD, DM or hyperlipidaemia. The most prevalent CVD-related comorbidity in patients with AS was hypertension [(35 (37.2%) patients *vs.* 96 (25.5%), matched p = 0.03)], with similar results seen in patients with PsA [41 (38.7%) patients vs. 114 (26.9%) matched (p = 0.02)]. The least prevalent CVD-related comorbidity was IHD [(10 (10.6%) patients *vs.* 36 (9.6%) matched p = 0.70)], with similar results seen in patients with PsA [10 (9.4%) patients vs. 32 (7.5%) matched (p = 0.55)]. No significant difference was

observed in the rates of CVD-related comorbidity in patients with Ps alone compared to their matched cohort.

Discussion

Given the increased rates of cardiovascular disease in patients with inflammatory disorders, it is increasingly important to monitor cardiovascular comorbidities [17]. Within this UK primary care consultation database, the rates of hypertension were significantly greater in those with AS and PsA compared to matched cohorts, although the prevalence of ischaemic heart disease, diabetes mellitus or hyperlipidaemia was similar between the AS and PsA cohorts compared to their matched cohorts. No differences were observed in the prevalence of any of the CVD-related comorbidities between patients with psoriasis and their matched cohort.

Our findings around increased prevalence of hypertension in patients with AS confirm those observed in a Welsh primary care AS cohort [9] and also those from Dutch secondary care [6]. Castañeda et al. also examined hypertension in both AS and PsA patients from the Spanish population and though found prevalence rates of 26% & 30% respectively, after multivariate analysis only PsA was significant ($p = <0.05$) compared to controls [18]. A cross-sectional secondary care sample from Belgium also found the prevalence of hypertension (32.8%) to be significantly greater in PsA patients than those with related, but non-PsA forms of spondyloarthritis [19]. Though these previously reported proportions of PsA patients with hypertension are lower than our reported 39% prevalence, our value is comparable to that found by Ernste et al. in a PsA cohort (n =158) from the Framington study, who found the prevalence of hypertension in this sample from the general population to be 37% [20]. Therefore our findings would infer prevalence rates of hypertension in AS and PsA patients for UK primary care (37% & 39% respectively) are broadly similar to other reports [6, 9, 19, 20]. Within our Ps cohort, although the prevalence of hypertension (23%) was comparable to that from other UK data (25%) [21], this was not different from the matched controls. Our finding contradicts a previous meta-analysis, which found an association between Ps and hypertension

[22]. However, since the meta-analysis found the strength of this association to be related to the severity of Ps, our lack of association may be related to using a primary care cohort with Ps, who are likely to have a range of disease severity. By examining the CVD-related comorbidities in a Ps sample as well as a PsA sample this provides an indirect comparison between the two. Our findings suggest that when considering CVD-related comorbidities in Ps patients, it may be worth focusing on the presence of hypertension in the subset with PsA.

To summarise, our results provide a UK primary care context to the increasing evidence that hypertension is common amongst patients with AS and PsA and further support the need to screen these patients for hypertension to reduce their CVD risk. In contrast, we did not find the prevalence rates of the other CVD-related comorbidities to be significantly different from their matched cohorts. For IHD, our findings were in contradiction to previous studies. In 2006, Han et al found a moderate increase in the prevalence of IHD in AS patients from a US health insurance database, reporting a relative risk of 1.2 (95% CI 1.0-1.5) [23]. In another study, though specific to myocardial infarction (MI), Peters et al reported a strong association between AS and an increased prevalence of MI in Dutch females matched to the general population (5.75 (2.1 to 15.8)), but no association for males (1.60 (0.9 to 2.8)) [10].

Currently the data regarding associations with diabetes is contradictory with some studies suggesting diabetes is common for both PsA [23, 24] and Ps patients [25], whilst other data, including our own, showed no association [18]. This may be related to variation in the study designs and the populations used. Similarly with hyperlipidaemia some studies have shown an association with AS and PsA [24] and others have shown no association [9]. In part, these findings may again be explained by differences in the populations studied and that patients with more severe disease may be at the greatest risk.

Strengths & Limitations

This study utilised a primary care consultation database (CiPCA) with high quality coding of clinical activity to compare the prevalence of CVD-related comorbidity in several inflammatory conditions with matched cohorts, an under researched area in this population. This study of CVD-related comorbidity in AS and PsA in UK primary care provides additional evidence to the potential problem of CVD comorbidity in these populations and provides an indirect comparison between PsA and Ps, two strongly related conditions.

Limitations of CiPCA include small patient numbers for each of these low prevalence inflammatory conditions. Ideally, we would have also wanted to assess data regarding smoking and BMI; however, these data are not routinely coded in primary care consultations and therefore would have been incomplete. We also acknowledge that the diagnosis of AS, PsA and Ps may not have been accurate in all patients, but the validity of coding within the CiPCA database is maintained at a high level and any such proportion would undoubtedly be small. We were unable to consider confounding variables in addition to those of age and gender, which were adjusted for within the matching process, due to the small sample size. Therefore, residual confounders, such as deprivation level or BMI may still be present within our analysis. Finally, as our data ranges from 1999-2009, there is the potential that the general practice coding of CVD-related comorbidity may vary over this period, due to increasing awareness of the link between inflammation and poor CVD outcomes. However, such an extensive period of data collection is necessary to allow enough time for the development of the study outcomes of interest and if anything, the use of an older dataset may suggest an underestimating of CVD-related comorbidity compared to present levels due to the current increased awareness amongst health professionals.

Conclusion

Our findings provide an additional comparison of the prevalence of CVD-related comorbidities, in three inflammatory conditions, in a UK primary care population. Patients with AS and PsA

have higher rates of hypertension compared to matched controls, although the rates in patients with Ps alone were similar to those in controls. Our findings add to the continuing debate concerning inflammatory musculoskeletal disease and the extent of CVD comorbidity. This further supports the argument for more evidence in the need for screening and intervention around CVD comorbidities, for each condition, to reduce the burden of CVD in these patients.

Acknowledgements: I would like to thank the Keele GP Research Partnership and the Informatics team at the Arthritis Research UK Primary Care Centre for providing the CiPCA dataset. CiPCA is funded by the North Staffordshire Primary Care Research Consortium and Keele University Institute for Primary Care and Health Sciences.

Competing Interests: The authors declare they have no conflicts of interest

Author Contributions: Contribution statement: Guarantor of overall study integrity: JAP, RH, CDM & SH. Study concept & design: JAP, RH & SH. Data collection and interpretation: NA, YC & JAP. Statistical analysis NA, YC & JAP. Manuscript preparation: NA, JAP, YC, RH, CDM & SH. Final approval of manuscript: NA, JAP, YC, RH, CDM & SH

Funding: JAP is funded by a Launching Fellowship from the NIHR School for Primary Care Research. CDM is funded by the National Institute for Health Research (NIHR) Collaborations for Leadership in Applied Health Research and Care West Midlands, the NIHR School for Primary Care Research and a NIHR Research Professorship in General Practice (NIHR-RP-2014-04-026). The study sponsors had no role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the NIHR (UK). This paper presents independent research which is part-funded by the CLAHRC West Midlands. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Ethics, consent and permissions

The CiPCA dataset (and any subsequent studies) was granted ethical approval by the North Staffordshire Research Ethics Committee.

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Table 1: Study sample characteristics

Characteristics	AS (n = 94)	Matched cohort (n = 376)	p value	PsA (n = 106)	Matched cohort (n = 424)	p value	Ps (n = 290)	Matched cohort (n = 1160)	p value
Age, (mean) years (SD)	58.8 (12.6)	58.8 (12.6)	-	59.5 (13.8)	59.5 (13.7)	-	57.5 (17.5)	57.5 (17.4)	-
Sex, male n (%)	82 (87.2)	328 (87.2)	-	51 (48.1)	204 (48.1)	-	130 (44.8)	520 (44.8)	-
Hypertension, n (%)	**35 (37.2)**	**96 (25.5)**	**0.03**	**41 (38.7)**	**114 (26.9)**	**0.02**	67 (23.1)	282 (24.3)	0.70
IHD, n (%)	10 (10.6)	36 (9.6)	0.70	10 (9.4)	32 (7.5)	0.55	17 (5.9)	73 (6.3)	0.89
Diabetes mellitus, n (%)	10 (10.6)	33 (8.8)	0.55	12 (11.3)	31 (7.3)	0.23	16 (5.5)	72 (6.2)	0.78
Hyperlipidaemia, n (%)	11 (11.7)	34 (9.0)	0.44	12 (11.3)	30 (7.1)	0.16	23 (7.9)	97 (8.4)	0.91

Ankylosing Spondylitis (AS), Psoriatic Arthritis (PsA), Psoriasis (Ps), Ischaemic Heart Disease (IHD), Standard Deviation (SD); p value obtained from χ^2 test. Significant values in **bold**